PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Suthanthiran, M.	Examiner:	Anne Holleran
Serial No:	09/780,953	Group Art Unit:	1642
Filed:	February 9, 2001	Docket:	955-3P/CON
For:	USE OF TGF-β ANTAGONISTS TO INHIBIT TUMOR CELL FORMATION OR PROGRESSION	Dated:	September 28, 2003

#14
10/16/03

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MANIKKAM SUTHANTHIRAN M.D. AND MINORU HOJO M.D., Ph.D. UNDER 37 C.F.R §1.131

Sir:

We, Manikkam Suthanthiran, M.D., holding the position of Transplantation Physician In Chief in the Department of Transplantation Medicine and Extracorporeal Therapy, and Chief of the Division of Nephrology, and Departments of Medicine and Surgery, Weill Medical College of Cornell University, 525 East 68th Street, New York, NY 10021, USA, and Minoru Hojo, MD, Ph.D., holding the position of Medical Director in Clinical Research Institute, BANYU Pharmaceutical, AIG Kabutocho Building, 5-1, Nihombashi-Kabutocho, Chuo-ku, Tokyo 103-0026, Japan, declare as follows:

1. We are joint inventors of the above-captioned patent application.

2. We are aware that the application was rejected over an article by Hutchinson et al (*Rev. in Immunogenetics*, 1:323-333) published on November 8, 1999, and also rejected over an article by Novak (*Nature Medicine* 5(4):382) published in April 1999 in view of Ohmori et al. (*Curr. Opin. Nephrol. Hypertens.* 7:539-545, 1998).

3. The claimed invention in the above-captioned application is described in the research paper entitled, "Cyclosporine induces cancer progression by a cell-autonomous mechanism" by Hojo et al., published in *Nature*, in the February 11, 1999 issue, volume 397, pages 530-534.

4. We are co-authors of the above-referenced publication of Hojo et al.

5. The conception of the present invention of a composition comprising a pharmaceutically effective amount of a TGF-β antagonist and an immunosuppressive agent was disclosed in the Hojo et al. article in the statement at page 533, in the first column, last paragraph:

> We investigated the effect of anti-TGF-β antibodies (1D11.16 IgG_1) on the cyclosporine-induced increase in the metastases to determine whether *in vivo* tumour progression by cyclosporine was dependent on TGF-β_1. Anti- TGF-β antibodies, but not control antibodies, prevented the cyclosporine-induced increase in metastases. (Citation omitted).

6. A reduction of the claimed invention to practice is apparent from the Hojo et al. article in the experiment described at page 533, bridging the first and second columns. The experiment demonstrates the induction of metastases by cyclosporine as well as a reduction in the number of metastases by an anti-TGF-β antibody after induction by cyclosporine in SCID-beige mice (that have little or no immune system function). In relevant part, this paragraph states:

> The number of pulmonary metastases was 350 ±22 (mean ± s.e.m., n=12) in control mice, 441 ± 20 (n=10) in cyclosporine-treated mice, 284 ±34 (n=8) in mice treated with cyclosporine and anti-TGF-β, and 490 ±56 (n=4) in mice treated with cyclosporine and control IgG_1 (P=0.0005; one-way ANOVA). The reduction in the number of metastases found following the administration of anti-TGF-β antibodies to cyclosporine-treated mice was significant at P<0.01 by ANOVA (Bonferoni P-value). In contrast, there was no

significant difference between the number of metastases found in mice treated with combined cyclosporine and control IgG_1 ($P>0.05$).

7. The Declaration of Dr. Suthanthiran under 37 C.F.R. 1.132 in accord with *In re Katz* filed with the amendment dated March 18, 2003 establishes that the above-referenced publication of Hojo et al. is a publication of the present inventors and others, and discloses the presently claimed invention.

8. Thus, the claimed subject matter of the above-captioned application was conceived and reduced to practice by us prior to November 8, 1999, the publication date of Hutchinson et al.

9. Furthermore, the claimed subject matter of the above-captioned application was also conceived and reduced to practice by us prior to April 1999, the publication date of Novak.

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: _____

M. Suthanthiran, M.D.

Dated: Sept 28, 2003

Minoru Hojo, M.D., Ph.D.

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Filed:	February 9, 2001	Docket:	955-3P/CON
For:	USE OF TGF-β ANTAGONISTS TO INHIBIT TUMOR CELL FORMATION OR PROGRESSION	Dated:	September 19, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Sir:

We, Manikkam Suthanthiran, M.D., holding the position of Transplantation Physician In Chief in the Department of Transplantation Medicine and Extracorporeal Therapy, and Chief of the Division of Nephrology, and Departments of Medicine and Surgery, Weill Medical College of Cornell University, 525 East 68th Street, New York, NY 10021, USA, and Minoru Hojo, MD, Ph.D., holding the position of Medical Director in Clinical Research Institute, BANYU Pharmaceutical, AIG Kabutocho Building, 5-1, Nihombashi-Kabutocho, Chuo-ku, Tokyo 103-0026, Japan, declare as follows:

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We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: 9/19/03

M. Suthanthiran, M.D.

Dated:_____

Minoru Hojo, M.D., Ph.D.

177995_1